



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/34, 9/00, 38/55	A1	(11) International Publication Number: WO 98/16252 (43) International Publication Date: 23 April 1998 (23.04.98)
(21) International Application Number: PCT/SE97/01652 (22) International Filing Date: 1 October 1997 (01.10.97) (30) Priority Data: 9603724-7 11 October 1996 (11.10.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LUNDGREN, Anna [SE/SE]; Topeliusgatan 4, S-412 68 Göteborg (SE). SKANTZE, Urban [SE/SE]; Östersnäs vägen 30, S-431 36 Möln dal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NEW PHARMACEUTICAL PARENTERAL FORMULATION OF A THROMBIN INHIBITOR (57) Abstract A pharmaceutical formulation of a thrombin inhibitor for parenteral use having an extended release effect, as well as a process for its preparation and the use of the formulation in arterial and/or venous thromboembolism, the extended release formulation comprising a thrombin inhibitor selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts, and one or more block copolymer having the general formula: $\text{HO}[\text{C}_2\text{H}_4\text{O}]_a[\text{C}_3\text{H}_6\text{O}]_b[\text{C}_2\text{H}_4\text{O}]_a\text{H}$, wherein each a independently is an integer 1 - 250 and b is an integer 1 - 250 and wherein the formulation has a solution-gelation transition temperature below 37 °C.		

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NEW PHARMACEUTICAL PARENTERAL FORMULATION OF A THROMBIN INHIBITOR

Field of invention

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The present invention relates to a new pharmaceutical formulation of thrombin inhibitors for parenteral use, which is an extended release formulation. The invention also relates to a process for the manufacture of such a formulation and, the use of the new formulation in medicine.

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Background of the invention

Thrombin inhibitors are effective for treatment of a number of diseases characterized by hypercoagulation.

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The compounds melagatran and inogatran are low- molecular weight, water soluble thrombin inhibitors with short half lives. To permit administration at a low frequency an extended release formulation is useful.

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Parenteral extended release formulations allow a drug to be delivered at controlled rate resulting in a satisfactory plasma concentration for an extended period of time, with less frequent administration, avoiding high peak blood concentrations. Particularly for low molecular weight, water soluble drugs with a short half life, an extended release effect may be a prerequisite for subcutaneous or intramuscular treatment.

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A wide range of measures are used to achieve extended release parenteral formulations.

30

One approach is to retard the diffusion of the drug out of the formulation. This can be achieved, for example by using a vehicle with increased viscosity. Another approach is to make a suspension of the drug, or a suitable salt of the drug, which is insoluble in the

vehicle and only sparsely soluble in the surrounding tissue after injection; the rate of dissolution of the drug is retarded and thereby the uptake of the drug.

Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers primarily used in pharmaceutical formulations as emulsifying, stabilising, or solubilizing agents (Tarcha, P, J., Polymers for controlling drug delivery, CRC press 1991.).

All poloxamers are chemically similar in composition differing only in the relative amount of ethylene and propylene oxide units and in the total molecular weight of the polymer. Some poloxamers are thermo-reversible in the temperature range around body temperature. A water solution of the compound is in the liquid state below the solution-gelation transition temperature, and a semi-solid gel above this temperature. Parameters that determine the formation and the viscosity of the gel can be the type of poloxamer used, the concentration of the poloxamer as well as the overall composition of the formulation (Schmolka I.R. Artificial Skin I. Preparation and properties of Pluronic F 127 gels for treatment of burns. J. Biomed. Mater. Res., 6 571, 1972). The potential use of poloxamers in drug delivery systems for extended release has previously been illustrated (US Patent No 4 474 752).

US 5 306 501 discloses certain poloxamers as a drug delivery system for drug injection for certain classes of drugs. The composition of the US 5 306 501 is said to provide a physiologically acceptable media having a buffered pH and an osmotically balanced vehicle so as to provide an isotonic mixture having iso-osmotic and pH properties which are similar to that of body fluids, such as blood plasma.

25

WO 95/151 82 discloses certain poloxamers in pharmaceutical composition either alone or in combination with an antibiotic for the treatment of infections.

US 5 306 501 and WO 95/15182 do not refer to the application of poloxamer in pharmaceutical formulations in order to obtain an extended release effect. This is

30

mentioned in US 4 474 752 which, however, refers to substantially different structures, which are substituted derivatives of ethylene diamine.

In Johnston et al. (Johnston, T.P. et al. J. of Parenteral Science & Technology, vol. 43, No. 6, 1989) and Pec et al. (Pec, E. A. et al. J. of Pharmaceutical Sciences, 81, 7, 1992)

Poloxamer 407 is suggested as a vehicle for obtaining in vivo extended release of the high molecular weight compounds inulin and urease. The highly viscous poloxamer matrix retards the diffusion of the large molecules through the formulation and extended release is obtained.

For low molecular weight compounds, diffusion is much more difficult to retard, which makes the viscosity properties (and the solution-gelation transition temperature) of the poloxamer vehicle particularly important for obtaining extended release effects in vivo. These parameters are determined by the overall composition of the formulation, such as the nature and concentration of the active compound, and the poloxamer, electrolytes, solvents, and surfactants, and it is not possible to predict the total effect on these parameters (Schmolka I.R. Artificial Skin I. Preparation and properties of Pluronic F 127 gels for treatment of burns. J. Biomed. Mater. Res., 6 571, 1972).

Guzman et al. International J. of Pharmaceutics, 80 (1992) p 119-127) illustrated how poloxamers can be used as extended release formulations for a model drug compound phenolsulfophtalein. Variations in gelation properties of the poloxamer formulations were found to be a function of the concentration of the model drug, as well as of the type and concentration of poloxamer and electrolyte.

Disclosure of the invention

The solution-gelation transition temperature and the viscosity in vivo in a poloxamer-containing extended release pharmaceutical formulation are determined by the overall composition of the formulation where the nature and concentration of the active compound, the poloxamer as well as e.g. additional electrolytes, surfactants, solvents, and

pH regulating agents are of major importance. The effect on viscosity parameters and the solution-gelation transition temperature due to interaction between a particular compound, and the formulation components is not predictable and thus not the in vivo extended release effect.

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It has now surprisingly been found that a formulation comprising a water solution of a low molecular weight, water soluble thrombin inhibitor with a short half life selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts and an additive selected from the group consisting of a block copolymer

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having the general formula

$$\text{HO}[\text{C}_2\text{H}_4\text{O}]_a [\text{C}_3\text{H}_6\text{O}]_b [\text{C}_2\text{H}_4\text{O}]_a \text{H}$$

wherein a is an integer 1-250 and b is an integer 1-250, and wherein the additive(s) together with the trombin inhibitor in the formulation have a solution-gelation transition temperature below 37°C, provides an extended release effect in vivo after subcutaneous

15

administration.

Melagatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cgl-Aze-Pab}$ (disclosed in EP 701 568) and inogatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cha-Pic-Nag}$ (disclosed in EP 618 926), wherein

20

Aze is (S)-azetidine-2-carboxylic acid

Cgl is (S)-cyclohexylglycine

Cha is (S)-β-cyclohexyl alanine

Nag is noragmatine

Pab is 1-amidino-4-aminomethyl benzene

25

Pic is (S)-pipecolic acid.

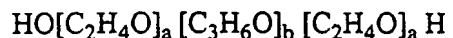
Physiologically acceptable salts may be any of the following salts of inorganic and organic acids, namely hydrobromide, hydrochloride, sulphate, nitrate, salts from sulphonic acids, e.g. methane sulphonate, ethane sulphonate, benzene sulphonate, toluene sulphonate,

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'naphthalene-2-sulphonate, salts from carboxylic acids, e.g. maleate, benzoate, salicylate,

acetate, malate, succinate, gluconate, glycollate, lactate, tartrate, citrate, ascorbate, hexanoate, octanoate, decanoate, undecylenate, dodecylsulphate, oleate, stearate.

As additives are used poloxamers, which are block copolymers having the general
5 formula



wherein a is an integer 1-250 and b is an integer 1-250.

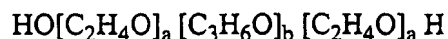
The additive(s) could be a single poloxamer or a mixture of two or more poloxamers.

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The preferred poloxamers have the general formula defined above wherein a is an integer 5 -150 and b is an integer 15-75.

The most preferred poloxamers have the general formula defined above wherein a is an
15 integer 70-105 and b is an integer 25-70.

Poloxamer 188 is a block copolymer having the general formula

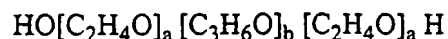


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wherein a is approximately 79 and b is approximately 28, having a molecular weight in the range of 7689-9510 and with a mass fraction of polyoxyethylene of approximately 81%.

Poloxamer 407 is a block copolymer having the general formula

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wherein a is approximately 98 and b is approximately 67, having a molecular weight in the range of 9840-14600 and with a mass fraction of polyoxyethylene of approximately 73%.

The concentration of the thrombin inhibitor is preferably in the range 0.01-20% (w/w), and more preferably 0.1-10% (w/w) of the ready to use formulation.

- 5 The concentration of the poloxamer is preferably 15-40 % (w/w), and more preferably 20-35% (w/w) but most preferably 25-30% (w/w) of the ready to use formulation.

The solution-gelation transition temperature of the ready to use formulation is below 37°C, preferably in the range 15-37° C and most preferably in the range 25-35°C.

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Due to physiological considerations a pH between 3-10 is preferred. If necessary the pH is adjusted with an acidifying agent, such as for instance acetic acid, ascorbic acid, citric acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid or tartaric acid, or an alkalising agent, such as sodium hydroxide.

15

The formulation may contain further additional components, such as antioxidants, antimicrobial preservatives, tonicity modifiers and/or buffer components.

20

The formulation is prepared conveniently by dissolving the solid components in water, adjusting the pH and sterilizing the resulting solution. The order in which the components are dissolved and at which stage the pH adjustment or sterilization is performed is not critical and may be chosen according to what is most suitable.

25

Suitable daily parenteral doses for the thrombin inhibitor in the therapeutical treatment of humans are 0.001-50 mg/kg body weight, preferably 0.005-5 mg/kg.

The pharmaceutical formulation is intended for prophylaxis and/or treatment in arterial as well as venous thromboembolism.

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The formulation is intended for parenteral use, including intracutaneous, subcutaneous, intra lipomateus, intra muscular and intraperitoneal administration.

Working examples**Example 1** (20 mg/ml Melagatran in 18/10% (w/w) of Poloxamer 407/188)

5	Melagatran	8.1 g
	Poloxamer 407	72 g
	Poloxamer 188	40 g
	HCl to adjust pH to 5	qs
	Water for injection to	400 g

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The poloxamers are weighed and slowly added to the main part of the water during intense stirring. When the poloxamers are dissolved the solution is filtered through 0.45 µm sterile filters. The weighed amount of melagatran is added to and dissolved in the poloxamer solution. The pH of the solution is adjusted to 5 with HCl and the rest of the water is added
15 to the final weight. The solution is sterilized by filtration through 0.22 µm sterile filters and filled into sterile injection vials.

The solution-gelation transition temperature of the formulation was determined as 34°C.

20 In similar ways the following formulations were prepared:

Example 2 (30 mg/ml Melagatran in 25% (w/w) of Poloxamer 407)

	Melagatran	450 mg
25	Poloxamer 407	3.75 g
	Water for injection to	15.0 g

The solution-gelation temperature of the formulation was determined as 17°C.

Example 3 (24 mg/ml Melagatran in 17/17 % (w/w) of Poloxamer 407/188)

	Melagatran	727 mg
	Poloxamer 407	5.1 g
	Poloxamer 188	5.1 g
5	HCl to adjust pH to 5	qs
	Water for injection to	30.0 g

The solution-gelation transition temperature of the formulation was determined as 32°C.

Example 4 (12 mg/ml Melagatran in 16% (w/w) of Poloxamer 407)

10	Melagatran	363 mg
	Poloxamer 407	4.8 g
	HCl to adjust pH to 5	q.s.
	Water for injection to	30.0 g

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The solution-gelation transition temperature of the formulation was determined as 30°C.

Example 5 (24 mg/ml Melagatran in 18% (w/w) of Poloxamer 407)

	Melagatran	727 mg
20	Poloxamer 407	5.4 g
	HCl to adjust pH to 5	q.s.
	Water for injection to	30.0 g

The solution-gelation transition temperature of the formulation was determined as 24°C.

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Biological experimentsData from pigsExtended release

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A dose of 30 mg of melagatran was administered subcutaneously to pigs in the poloxamer-containing formulation of Example 2 and in a physiological saline solution. Data shows an obvious extended release effect and a reduced peak plasma concentration for the formulation according to the invention as compared to the formulation comprising a physiological saline solution. The plasma concentration was followed during the first 4 hours.

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Physiological saline vehicle Poloxamer vehicle

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Time (minutes)	Mean plasma concentration (μ mole/l) N=3	Mean plasma concentration (μ mole/l) N=3
0	0.00	0.00
10	1.11	0.10
20	1.80	0.29
40	1.19	0.30
60	0.89	0.27
90	0.57	0.30
120	0.41	0.35
240	0.12	0.38

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Data from humansExtended release

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A dose of 5 mg of melagatran was administered subcutaneously to humans in the poloxamer-containing formulation of Example 1, and in a physiological saline solution.

Data shows a 3-fold decrease in absorption rate and a reduced peak plasma concentration for the formulation according to the invention as compared to the formulation comprising a physiological saline solution.

5

Poloxamer vehicle			Physiological saline vehicle		
	Time	Mean plasma concentration		Time	Mean plasma concentration
		N = 6			N = 6
10	(minutes)	(μ mole/litre)		(minutes)	(μ mole/litre)
	5	- xx)		5	0.084
	10	- x)		10	0.23
	15	- x)		15	0.43
15	20	0.25		20	- x)
	30	- x)		30	0.59
	40	0.36		40	-
	45	- x)		45	0.55
	60	0.40		60	0.49
20	90	0.41		90	0.37
	120	0.34		120	0.28
	150	0.28		150	- x)
	180	0.23		180	0.19
	210	- x)		210	0.15
25	240	0.16		240	0.12
	300	0.10		300	0.085
	360	0.063		360	- x)
	480	0.028		480	0.024
	600	0.016		600	- x)
30	720	0.011		720	- x)

The total area under the plasma concentration versus time curves are equal for the two formulations ($AUC=88.3 \mu\text{mole} \cdot \text{L}^{-1} \cdot \text{min.}$)

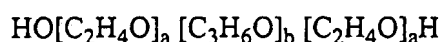
x) not determined

35 xx) below limit of quantitation

The data set out above from pigs and humans clearly demonstrate a significant and useful extended release effect achieved by the present invention.

Claims

1. An extended release formulation for parenteral administration of a water solution of a low molecular weight water soluble thrombin inhibitor with a short half life comprising a thrombin inhibitor selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts, and one or more block copolymer having the general formula



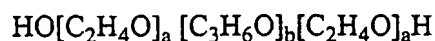
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wherein each a independently is an integer 1-250 and b is an integer 1-250 and wherein the formulation have a solution-gelation transition temperature below 37°C.

2. A formulation according to claim 1, having at least one additional component which is an acidifying or alkalising agent, antimicrobial preservative, tonicity modifier, antioxidant and/or buffer.

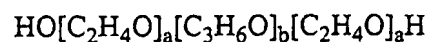
3. A formulation according to claim 1 or 2, wherein the block copolymer has the general formula

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wherein each a independently is an integer 5-150 and b is an integer 15-75.

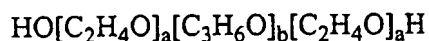
4. A formulation according to claims 1 or 2, wherein the additive is a block copolymer having the general formula



wherein each a independently is an integer 70-105 and b is an integer 25-70.

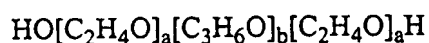
25

5. A formulation according to any one of claims 1 to 4, wherein the additive is a block copolymer having the general formula



5 wherein each a is approximately 79 and b is approximately 28, having a molecular weight in the range of 7689-9510 and with a mass fraction of polyoxyethylene of approximately 81%.

10 6. A formulation according to any one of claims 1 to 4, wherein the additive is a block copolymer having the general formula



15 wherein each a is approximately 98 and b is approximately 67, having a molecular weight in the range of 9840-14600 and with a mass fraction of polyoxyethylene of approximately 73%.

20 7. A formulation according to any of the preceding claims wherein the additive is a mixture of the block copolymers defined in claim 5 and claim 6.

8. A formulation according to any one of claims 1 to 7, wherein the additive(s) together with the thrombin inhibitor in the formulation have a solution-gelation transition temperature within the range 15-37°C.

25 9. A formulation according to claim 8, wherein the additive(s) together with the thrombin inhibitor in the formulation have a solution-gelation transition temperature within the range 25-35°C.

10. A formulation according to any one of claims 1 to 9 wherein the thrombin inhibitor is melagatran or a physiologically acceptable salt thereof.
11. A formulation according to any one of claims 1 to 10 wherein the concentration of the
5 thrombin inhibitor is in the range 0.01 - 20 % (w/w) of the ready to use formulation.
12. A formulation according to claim 11 wherein the concentration of the additive(s) is 15
- 40 % (w/w) of the ready to use formulation.
- 10 13. An extended release formulation as defined in any of claims 1-12 for use in the prophylaxis and/or treatment in arterial and/or venous thromboembolism in mammals including man.
14. A process for the preparation of a formulation according to any of the preceding claims
15 wherein the thrombin inhibitor and the additives are dissolved in water, the pH is adjusted and the resulting solution is sterilized, the separate steps being performed in any order.
15. A method for the prophylaxis and/or treatment of arterial and/or venous thromboembolism in mammals including man by administering to a host in need thereof of
20 a formulation as defined in any of claims 1-13.
16. Use of the components of the extended release formulation defined in any one of claims 1 to 13 for the manufacture of a medicament useful in the prophylaxis and /or treatment of arterial and /or venous thromboembolism.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01652

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 47/34, A61K 9/00, A61K 38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPIL, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, File 155, MEDLINE, Dialog accession no. 07242053, Medline accession no. 93020237, Pec EA et al: "Biological activity of urease formulated in poloxamer 407 after intra- peritoneal injection in the rat"; & J Pharm Sci (UNITED STATES) Jul 1992, 81 (7) p626-30 --	1-16
X	Dialog Information Services, File 155, MEDLINE, Dialog accession no. 05731289, Medline accession no. 90095751, Johnston TP et al: "Inulin disposi- tion following intramuscular administration of an inulin/poloxamer gel matrix"; J Parenter Sci Technol (UNITED STATES) Nov-Dec 1989, 43 (6) p279-86 --	1-16

☒ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1998	06 -02- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01652

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9429336 A1 (ASTRA AKTIEBOLAG), 22 December 1994 (22.12.94), claims 25-26 --	1-16
A	WO 9311152 A1 (AKTIEBOLAGET ASTRA), 10 June 1993 (10.06.93), claims --	1-16
A	DE 2233816 A (BASF WYANDOTTE CORP.), 1 February 1973 (01.02.73) --	1-16
A	US 5306501 A (TACEY X. VIEGAS ET AL), 26 April 1994 (26.04.94) -- -----	1-16

INTERNATIONAL SEARCH REPORT

Search request No.

SE 96/01104

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international-type search report has not been established in respect of certain claims for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claim 15 is directed to a method of treatment of the human or animal body by a therapy method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compositions.
2. ☐ Claims No.:
because they relate to parts of the national application that do not comply with the prescribed requirements to such an extent that no meaningful international-type search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this national application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international-type search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international-type search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international-type search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

07/01/98

International application No.

PCT/SE 97/01652

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9429336 A1	22/12/94	AU 684086 B	04/12/97
		AU 6986994 A	03/01/95
		BR 9406746 A	19/03/96
		CA 2162900 A	22/12/94
		CN 1127509 A	24/07/96
		CZ 9503020 A	17/04/96
		EP 0701568 A	20/03/96
		FI 955828 A	04/12/95
		HR 940311 A	31/10/96
		HU 74739 A	28/02/97
		HU 9503445 D	00/00/00
		IL 109634 D	00/00/00
		JP 8511018 T	19/11/96
		LT 1947 A	27/12/94
		LT 3768 B	25/03/96
		MX 9404114 A	31/01/95
		NO 954873 A	01/02/96
		NZ 267534 A	22/08/97
		PL 311819 A	18/03/96
		SK 145495 A	01/10/96
		US 5602253 A	11/02/97
WO 9311152 A1	10/06/93	AP 353 A	14/08/94
		AP 9200457 D	00/00/00
		AU 670052 B	04/07/96
		AU 683793 B	20/11/97
		AU 3120993 A	28/06/93
		AU 5061696 A	01/08/96
		CA 2125175 A	10/06/93
		CN 1076199 A	15/09/93
		CZ 9401296 A	15/12/94
		CZ 9503338 A	17/04/96
		EP 0618926 A	12/10/94
		FI 942645 A	03/06/94
		HU 70431 A	30/10/95
		HU 9401474 D	00/00/00
		JP 9500356 T	14/01/97
		MX 9206938 A	01/06/93
		NO 942066 A	03/06/94
		NZ 246106 A	26/07/96
		SE 9103612 D	00/00/00
		SK 63194 A	07/12/94
		US 5614499 A	25/03/97
		ZA 9209099 A	07/06/93
DE 2233816 A	01/02/73	AU 445143 B	14/02/74
		AU 4379372 A	03/01/74
		CA 963389 A	25/02/75
		FR 2145568 A,B	23/02/73
		GB 1340294 A	12/12/73
		ZA 7204184 A	28/03/73

INTERNATIONAL SEARCH REPORT

Information on patent family members

07/01/98

International application No.

PCT/SE 97/01652

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5306501 A	26/04/94	CA 2040460 A,C	02/11/91
		DE 69124416 D,T	04/09/97
		EP 0455396 A,B	06/11/91
		SE 0455396 T3	
		JP 4225914 A	14/08/92
		US 5593683 A	14/01/97
